PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE
in its capacity as elected Office

Date of mailing (day/month/year) 07 February 2001 (07.02.01)	
International application No. PCT/AU00/00643	**Applicant's or agent's file reference** 2831WOP00
International filing date (day/month/year) 07 June 2000 (07.06.00)	**Priority date** (day/month/year) 07 June 1999 (07.06.99)
Applicant CLANCY, Robert et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

22 December 2000 (22.12.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer A. Karkachi
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 28317WOP00 DAA/JFO:NMT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. **PCT/AU00/00643**	International Filing Date *(day/month/year)* 7 June 2000	Priority Date *(day/month/year)* 7 June 1999
International Patent Classification (IPC) or national classification and IPC **Int. Cl.** [7] G01N 33/53, 33/68		
Applicant THE UNIVERSITY OF NEWCASTLE RESEARCH ASSOCIATES LIMITED *et al.*		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheet(s).

3. This report contains indications relating to the following items:

I	☒	Basis of the report
II	☐	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☒	Certain observations on the international application

Date of submission of the demand	Date of completion of the report
22 December 2000	21 September 2001
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **NORMAN BLOM** Telephone No. (02) 6283 2238

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU00/00643

I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed.

[ ] the description, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the claims, pages , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages , received on with the letter of

[ ] the drawings, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/fig.

5. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims **1-19**	**YES**
	Claims **none**	**NO**
Inventive step (IS)	Claims **1-19**	**YES**
	Claims **none**	**NO**
Industrial applicability (IA)	Claims **1-19**	**YES**
	Claims **none**	**NO**

2. Citations and explanations (Rule 70.7)

Novelty (N) and Inventive Step (IS): Claims 1-19

None of the documents cited in the ISR disclose a method of assessing potential susceptibility to development of ALTE and/or SIDS in a subject by determining the **immunoglobulin A (IgA) or immunoglobulin A1 (IgA1)** level in a sample from the subject and comparing this IgA level with that of a predetermined standard in order to predict susceptibility to development of ALTE and/or SIDS.

The closest prior art is to be found in the following three documents:-

US 5556759 and **US 5747266**, both of which disclose an assay and method for screening newborns to determine risk of SIDS based on the detection of elevated IgM-anti-IgG (MAG) levels in newborns' serum within the first year of birth.

Pediatric Research (1993), **33** (6), 554-556 discloses that an abnormal (exaggerated and prolonged) immune response was seen in an infant who unexpectedly died from SIDS following a transient mild URTI. The IgA level in the saliva of this infant was found to rise in the 4th week of life and continued to rise in samples collected in the 6th and 8th week to a level 5 times higher than the age-related median level for 8 weeks of age. It is noted that the appearance of IgM and an increase in IgA in saliva is a normal event after URTI (page 555 column 2) and it is indicated that a previous control study had found that the IgA **peak level** during URTI periods (in three children under 6 months of age) did not exceed 0.020 g/L (see page 555 column 1) (this peak IgA concentration during URTI is at odds with the age-related reference IgA concentrations depicted in the shaded areas in Figure 1 (C), which shows a 90th percentile reference level of 0.050-0.060 g (IgA)/L for infants between the ages of 3-8 weeks). Several other potentially conditionary risk factors (page 556 column 1) were identified in this SIDS infant (including passive smoking (page 554 column 2), a transient mild URTI (abstract, page 554 column 1 and page 555 column 2) and pattern of infant feeding (page 554 column 1)). It is postulated that a disturbance in immune regulation and/or mucosal permeability may constitute a link in the chain of events that lead to respiratory arrest (page 554 column 1) or that an inappropriate or persistent mucosal immune response to antigen may activate vagal afferent nerve endings or chemoreceptors to induce reflex apnea (page 556 column 1).

The following documents cited in the ISR disclose that elevated levels of IgA or IgA producing cell were found in serum, lung lavage or tissues from various organs following post mortem investigations of victims of SIDS.

Pediatric Research (1992), **31** (4), 372-375 discloses that the number of IgA plasma cells in duodenal mucosa from SIDS cases was significantly more than that found in non-infectious controls but on the other hand the number of IgA plasma cells in infants who died of infections was significantly more than than that of the SIDS cases (see page 373 *Results*). Further, although 90% of SIDS infants had definite signs and symptoms of an URTI none of these infections were judged to be sufficient to cause death (see page 373 column 2).(continued)

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 19 is not clear because it purports to define a kit yet it does not specify a single component of this kit.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of V. 2. Citations and explanations

Pediatr Allergy Immunol (1995), **6**, 48-55 discloses that the number of IgA cells was higher in SIDS vs. controls in both the germinal centre and in the interfollicular area of the palatine tonsils, while no differences could be demonstrated in the mantle zone or in the reticular epithelium (page 52 column 1). It is indicated that the palatine tonsils are not part of the secretory immune system but may play an important role in priming the BALT and GALT lymphoid systems (see pages 48-49). It is indicated that SIDS might be due to an overreaction of the mucosal immune system to a common microbial factor (see page 53 column 2 lines 29-39).

Journal of Pathology (1995), **177**, 415-421 discloses that peribronchial IgA expression was significantly increased in SIDS cases but that there was no significant difference in subpleural IgA expression between the SIDS group and controls (see page 419 column 1). This study also found that peribronchial IgA was the only immunoglobulin which showed increased expression in SIDS infants (see page 420) (which is indicated to be in conflict with reports of several other studies). It is indicated that increased IgA expression in peribronchial sites may contribute to pulmonary damage in SIDS (page 420).

BMJ (1989), 298, 23-26 discloses that victims of SIDS had grossly raised concentrations of IgG, IgM and to a lesser extent IgA compared with the controls. The mean IgA concentration in lung lavage samples taken from the SIDS group was significantly more than controls (7 g/mg total protein for SIDS victims compared with 3 g/mg in the controls) and pulmonary immunohistological staining revealed that the number of positively staining IgA bearing cells was significantly increased compared to controls (see Figures 2 and 3 and *Results* (page 24-25)).

J. Clin. Path., (1971), **24**, 736-739 discloses that in 18%, 21% and 67% of cases of SIDS, serum levels of IgA, IgG and IgM respectively, were higher than levels found in normal infants.

The Lancet (1990), **335** (8683), 229-230 discloses that SIDS victims had significantly increased numbers of IgG, IgM and IgA producing cells compared with non-infectious controls whereas the numbers of Ig producing cells in the infants that died from pneumonia were much the same as those in SIDS victims. These findings are said to suggest the possibility of immunological overstimulation in the upper respiratory and gastrointestinal tracts which ultimately leads to hypoxia and death (see entire letter to the Editor).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU00/00643

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: G01N 33/53, 33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Derwent (WPAT), Medline and chemical abstracts. Keywords (iga, immunoglobulin a, sids, sudden infant death, apnea, apnoea, alte, saliva)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Pediatric Research (1993), 33 (6), 554-556, *Mucosal Immune Response in a Case of Sudden Infant Death Syndrome*, M. Gleeson *et al.* (see entire article, particularly the Discussion on pages 555-556)	1-8, 10-19
Y	US 5556759 A (Beach P. G.) 17 September 1996 (see entire document, in particular column 1 lines 22-36 and column 2 lines 33-49)	1-19
Y	US 5747266 A (Beach P. G.) 5 May 1998 (see entire document, in particular column 1 lines 24-38 and column 2 lines 35-51)	1-19

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 August 2000	25 AGUS. 2000
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer **NORMAN BLOM** Telephone No : (02) 6283 2238

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU00/00643

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BMJ (1998 January), **298**, 23-26, *Lung immunoglobulins in the sudden infant death syndrome*, K. D. Forsyth *et al.* (see entire article, in particular the abstract, Introduction and Results qnd page 25 column 2)	1-9,11-14, 16-19
Y	Journal of Pathology (1995), **177**, 415-421, *Pulmonary Eosinophilia in Sudden Infant Death Syndrome*, J. A. Baxendine and I. E. Moore. (see entire document, in particular Figure 1, page 419 column 1 and page 420 column 1)	1-9, 11-14, 16-19
Y	The Lancet (1990 January 27), **335** (8683), 229-230, *Increased immune response in upper respiratory and digestive tracts in SIDS*, P. S. Thrane *et al.* (see entire Letter to the Editor)	1-19
Y	Pediatric Research (1992), **31** (4), 372-375, *Sudden Infant Death Syndrome Victims Show Local Immunoglobulin M Response in Tracheal Wall and Immunoglobulin A Response in Duodenal Mucosa*, L. Stoltenberg *et al.* (see entire article, in particular the abstract, page 372, page 373 "Results", and page 374 column 2)	1-9, 11-14, 16-19
Y	Pediatr. Allergy Immunol. (1995), **6**, 48-55, *Changes in the concentration and distribution of immunoglobulin-producing cells in SIDS palatine tonsils*, L. Stoltenberg *et al.* (see entire article, in particular pages 48-49 and 52-53)	1-9, 11-14, 16-19
Y	J. Clin. Path. (1971), **24**, 736-739, *Sudden unexplained death in infancy and hyperimmunization*, G. E. D. Urquhart *et al.* (see entire article)	1-4, 8, 10-11, 14, 16-17, 19
Y	Basic and Clinical Immunology, Seventh Edition (1991), Edited by Daniel P. Stites and Abba I. Terr, published by Appleton & Lange (a division of Prentice-Hall International Inc.), Chapter 15, *The Mucosal Immune System*, Pages 175-186. (see in particular page 179 and pages 183-184 column 1 "Mucosal Homing").	1-19
Y	Scand. J. Immunol. (1991), **33** (5), 533-541, *The Variability of Immunoglobulins and Albumin in Salivary Secretions of Children*, M. Gleeson *et al.* (see page 533 column 1, page 536 column 2 to page 537 column 1 and the abstract)	1-19
A	Clinics in Perinatology (1992), **19** (4), 809-838, *Apparent Life-Threatening Events and Apnea of Infancy*, J. G. Brooks (see page 819 "Clinical Presentation" (first paragraph), page 826 Table 15 "Acute Condition", page 829 "Management" (last paragraph)).	1
Y	Clinics in Perinatology, (1992), **19** (4), 861-869, *Prospective Identification of the Risk of SIDS*, D. C. Shannon (see page 862 lines 9-11)	1

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU00/00643

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member	
US	5747266	US	5556759
US	5556759	US	5747266

END OF ANNEX